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In Memoriam

# Dirk W. van Bekkum: Transplant Pioneer (1925-2015)

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Dirk van Bekkum was a pioneer of bone marrow transplantation who helped to establish and shape our discipline. His discoveries led the way to the clinical use of transplantation. Dirk was born in Batavia, the Dutch West Indies (Djakarta, Indonesia today) where his father was a civil servant. He was educated at Leiden University in The Netherlands and received his MD in 1950. He then studied biochemistry at Oxford with Sir Rudolph Peters and returned to The Netherlands to complete his PhD, cum laude, on the effect of corticosteroids on muscle development in 1952. In 1960, he founded the Radiobiological Institute of the Dutch Health Organization TNO in Rijswijk. Protection against radiation exposure had become a hot research topic after the atomic bombs were dropped on Hiroshima and Nagasaki at the end World War II. Protection of people from what was then termed *bone marrow syndrome*, resulting from radiation exposure, would become a focus of the Institute's research efforts for many decades.

Dirk's research contributions to the field of transplantation were fundamental. It is difficult to imagine, but at that time, the basis of the protective effect of a spleen cell or bone marrow transplantation after total body radiation was a mystery. Was it a humoral factor (hormone) in the donor bone marrow that protected and supported recovery of endogenous bone marrow cells, or was it something else? In 1956, van Bekkum and colleagues, simultaneously with scientists in Oxford and San Francisco, reported data supporting the notion that cells from the graft repopulated the host bone marrow tissue and were responsible for hematopoietic recovery from radiation-induced aplasia. They termed the outcome *chimerism* after the mythological Greek beast part lion, part goat, part snake. van Bekkum and colleagues then showed that the degree of donor engraftment and of chimerism depend not only on the intensity of myeloid and lymphoid suppression (conditioning) of the recipient, but also on numbers of spleen and/or bone marrow cells transplanted and on genetic relatedness between donor and recipient. They based the latter conclusion on comparisons of outcomes of isogeneic, syngeneic, and allogeneic transplantations. A *wasting syndrome*, then called *secondary disease*, characterized by weight loss, diarrhea, skin and fur abnormalities, and death had been described in mice surviving after a transplantation, but the etiology was unknown. Using parent to $F_1$ hybrid and the reverse donor-recipient transplantation combinations in mice, Dirk and colleagues proved that the secondary disease phenomenon was caused by graft-versus-host disease (GVHD), ie, donor immune cells in the graft reacting against recipient tissues. They also recognized that there is a quantitative relationship between numbers of transplanted, allogeneic immune cells and the incidence and severity of GVHD. Dirk discovered bone marrow from subhuman primates (*Rhesus* monkeys), like humans, contains many more immune cells, able to induce GVHD, compared with rodent bone marrow. This explains the marked differences in patterns of GVHD between these species. van Bekkum showed that in mice, and later in *Rhesus* monkeys and beagles, that selective elimination of PHA-reactive lymphocytes from the allogeneic graft could

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decrease or prevent GVHD. From 1966 to 1976, Dirk and his team showed antilymphocyte serum could be used to prevent or treat GVHD in mice and monkeys. This led to diverse uses of antilymphocyte serum in the transplantation setting. Another innovative field he pioneered was gnotobiology. van Bekkum and colleagues showed that host gastrointestinal flora, especially Gram-negative organisms, are important in the development of GVHD. Under some experimental conditions, GVHD could be prevented in germ-free mice. They also showed that in mice, dogs, and monkeys, bacterial decontamination before transplantation would reduce the incidence and severity of GVHD. This led to many of our current antimicrobial practices.

In 1967, van Bekkum, Jon van Rood, Leo Jan Dooren, and Jaak Vossen performed the first successful allotransplantation in humans in an infant with severe combined immune deficiency (SCID). SCID was a lethal disease with no effective therapy, and previous transplantation attempts in several settings and diseases had failed. Based on their observations in hematopoietic chimeras, neonatally thymectomized animals, and autopsy studies of children with SCID, van Bekkum and his team postulated that SCID resulted from a hematopoietic stem cell defect, resulting in failure of these cells to mature in the thymus into immune competent lymphocytes. They reasoned that children with SCID could be cured by providing a transplant of normal hematopoietic stem cells. The transplantation was done with bone marrow from an HLA-identical sibling, separated on a discontinuous density gradient to deplete cells able to cause GVHD, and the child was nursed in a laminar air flow room. Simultaneously, teams in Minneapolis (Robert Good, Richard Gatti, Hilaire Meuwissen, Richard Hong, and others) and Madison (Fritz Bach, Mortimer Bortin, and others) were also successful in curing children with SCID or the closely related Wiskott-Aldrich syndrome. Transplantation has became a standard treatment for children with SCID.

In 1971, after developing albumin density gradients and fluorescence activated cell sorting to concentrate stem cells, Van Bekkum and collaborators defined the morphological and submicroscopic features of hematopoietic stem cells in highly purified bone marrow fractions.

The Radiobiological Institute, under van Bekkum's leadership, would become one of the leading scientific centers, with important programs in bone marrow transplantation, stem cell, and experimental leukemia research. The atmosphere in the Institute bore the typical van Bekkum stamp. There was an ambitious spirit of team work and scientific entrepreneurship. Evening seminars, preceded by Indonesian rijsttafel (enthusiastically adopted by the Dutch), were famous and attracted attendees from far away, who did not want to miss the presentations and discussions (much less the food). There was much fun and humor in the air of the Institute. Cabarets were produced at party evenings; Dirk would play major roles. Table tennis during lunch would offer a popular break to staff, PhD and post-doctoral students, and technicians. Dick was a ping pong champion and enjoyed tennis, skiing, and swimming.

The international workshops Dirk organized at the Institute were intended to bring together scientists with opposing views and/or conflicting data. These were memorable. For instance, for the workshop on in vitro colony-forming cells held in 1971, in the early days of the emerging field of progenitor cell research (before the molecular cloning of the growth factors), researchers such as Ray Bradley, Don Metcalf, Malcolm Moore, Dov Pluznik, Ernest McCullough, John Till, Fred Stohlman, and others brought their culture systems with their impure ingredients (conditioned media, tissue extracts) to the Institute to do experiments and make direct comparisons.

In 1967, van Bekkum and Marco de Vries published *Radiation Chimeras*, the Bible of experimental bone marrow transplantation. The book describes the fundamentals of bone marrow transplantation, concepts of hematopoietic chimerism, GVHD, and potential clinical applications of transplantations. The authors predicted, 50 years ago, almost all areas we work in today!

Dirk had a unique personality. He liked debate and would challenge any speaker, regardless their position. However, he was straight and stimulated a critical discussion. He wanted to bring the real issues to the surface in the interest of clear thinking and conclusions. Beneath it all, he was kind, warm-hearted, and encouraging to students, colleagues, and friends.

Dirk was the mentor to one of us (B.L.). The first time I met with him was almost 45 years ago. In 1971, Professor van Bekkum's secretary led me to his office. I was 25 years old and had just graduated from medical school. We immediately got into a heated discussion over my possible research project. On leaving, I was convinced he would never accept my application for a postdoctoral position. But he did. That meeting was the beginning of my research career in hematology and of a lasting professional relationship and friendship.

Dirk received various honors. He was an elected member of the Dutch Royal Academy of Arts and Sciences and a Knight of the Royal Order of the Lion of The Netherlands, a founder of the European Organization for Research on Treatment of Cancer, European Bone Marrow Transplantation Group, the International Bone Marrow Transplantation Registry (now CIBMTR), the International Society of Experimental Hematology, the Dutch Society of Immunology, recipient of a Fogarty Scholarship from the US National Institutes of Health, and an honorary member of the Dutch Society of Gene Therapy and Cell Biology.

Dick is survived by his wife Ada, 4 daughters, 11 grandchildren, and 7 great grandchildren with more en route. He will be greatly missed by many people everywhere.